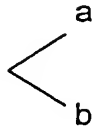


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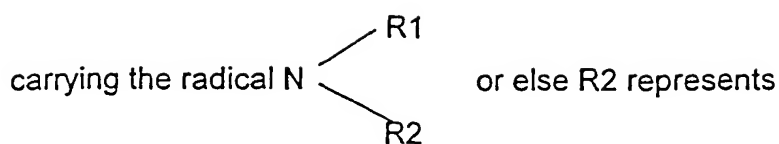
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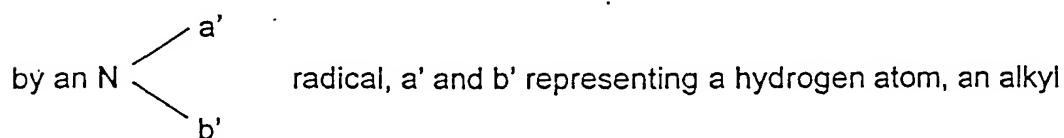
substituted by a



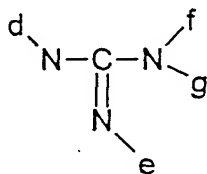
-or else R1 forms a double bond with the endocyclic carbon atom



an XR_a radical, X representing an oxygen atom or an NH or N-alkyl radical containing up to 8 carbon atoms and R_a represents a hydrogen atom, a linear, branched or cyclic alkyl radical containing up to 8 atoms of carbon optionally substituted by one or several halogen atoms, by one or several OH, CO_2H CO_2alc radicals,



radical containing up to 8 carbon atoms, a' and b' able to form a heterocycle optionally containing one or several additional heteroatoms and/or by a heterocycle containing one or several heteroatoms or R2 represents a radical



in which d, e, f, and g represent a hydrogen atom or an alkyl radical containing up to 8 carbon atoms, f and g able moreover to represent an acyl radical containing up to 8 carbon atoms, e and f able equally to form a ring optionally containing one or several heteroatoms,

R3 represents a hydrogen atom, a methyl or hydroxyl radical

R4 represents a hydrogen atom or a hydroxyl radical R representing a linear or branched or cyclic chain containing up to 30 carbon atoms, optionally containing one or several heteroatoms, one or several heterocycles or a linear, branched or cyclic acyl radical containing up to 30 carbon atoms

optionally containing one or several heteroatoms and/or one or several heterocycles,

T represents a hydrogen atom, a methyl radical, a CH_2CONH_2 , $\text{CH}_2\text{C}\equiv\text{N}$ radical, a $(\text{CH}_2)\text{NH}_2$ or $(\text{CH}_2)_2\text{Nalc}^+\text{X}^-$ radical, X being a halogen atom and also an alkyl radical containing up to 8 carbon atoms,

Y represents a hydrogen atom, a hydroxyl radical or a halogen atom or an OSO_3H radical or one of the salts of this radical,

W represents a hydrogen atom or an OH radical,

Z represents a hydrogen atom or a methyl radical, as well as the addition salts with the acids of the products of formula (I).

Amongst the addition salts with the acids, those formed with mineral acids, such as hydrochloric, hydrobromic, sulphuric or phosphoric acids or the organic acids like formic, acetic, trifluoroacetic, propionic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, alkanesulphonic, such as sulphonic methane or ethane, arylsulphonic acids like the benzene or paratoluenesulphonic acids can be cited.

In the definition of the substituents,

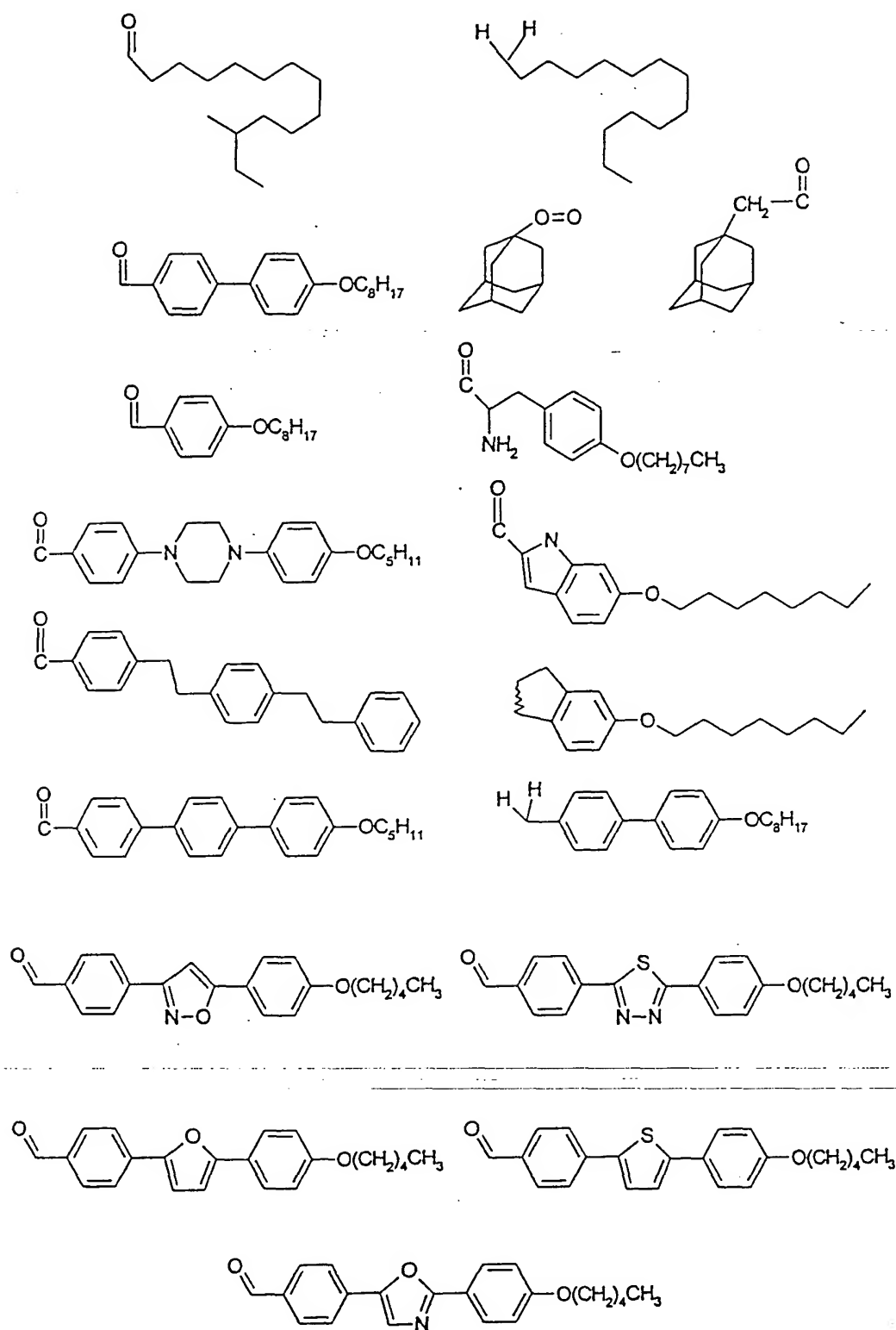
- the alkyl, alkenyl or alkynyl radical is preferably a methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, terbutyl, decyl or dodecyl, vinyl, allyl, ethynyl, propynyl, cyclobutyl, cyclopentyl, or cyclohexyl radical,
- the halogen is preferably fluorine or chlorine or bromine,
- the aryl radical is preferably the radical phenyl,
- the heterocyclic radical is preferably the pyrrolyle, pyrrolidinyl, pyridyl, pyrazinyl, pyrimidyl, piperidinyl, piperazinyl, quinuclidinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, imidazolyl, benzimidazolyl, triazolyl, thiazolyl, azetidyl, aziridinyl radical.

as a salt of the SO_3H radical, sodium, potassium salts or even the salts of amines can in particular be cited.

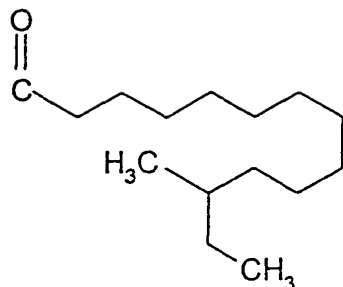
Amongst the preferred compounds of the invention:

- the compounds of formula (I), in which T represents a hydrogen atom,
- the compounds of formula (I), in which Y represents a hydrogen atom,
- the compounds of formula (I), in which W represents a hydrogen atom,
- the compounds of formula (I), in which Z represents a methyl radical,

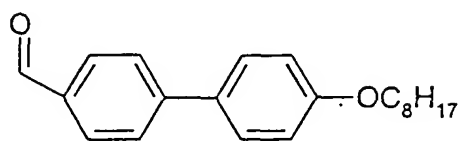
- the compounds of formula (I), in which R₃ represents a methyl radical,
 - the compounds of formula (I), in which R₄ represents a hydroxyl radical
 - the compounds of formula (I), in which R represents a radical
- can be especially cited.



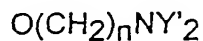
and more particularly those in which R represents a chain



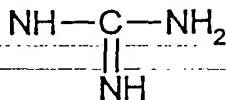
or those in which R represents a chain



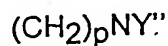
-the compounds of formula (I) in which R1 forms with the endocyclic carbon atom carrying the NR1R2 radical, a double bond, and notably those in which R2 represents the radical



in which n represents an integer between 1 and 8 and very particularly those in which n represents the number 2 and Y' represents a hydrogen atom or an alkyl radical containing up to 8 carbon atoms, and those in which R represents a radical



The invention has equally particularly as its object the compounds of formula (I) in which R2 represents a radical



in which Y'' represents a hydrogen atom or an alkyl radical containing up to 8 carbon atoms and p represents an integer varying from 1 to 8 and especially the compounds in which p represents the number 2.

The invention has very particularly as its object, compounds in which R1 represents a hydrogen atom.

Amongst the preferred compounds of the invention, the products of examples 8, 9, 11, 13 and 14 can be cited.

The compounds of formula (I) present significant anti-fungal properties; they are active notably on *Candida albicans* and other *Candida* like *Candida glabrata*, *krusei*, *tropicalis*, *pseudotropicalis*, *parapsilosis* and *Aspergillus fumigatus*, *Aspergillus flavus*, *Cryptococcus neoformans*.

The compounds of formula (I) can be used as medicines in man or animal, to fight against notably digestive urinary, vaginal or cutaneous candidoses, cryptococcoses, for example neuromeningeal, pulmonary or cutaneous cryptococcoses, bronchopulmonary and pulmonary aspergilloses and invasive aspergilloses of immunocompromise.

The compounds of the invention can be equally used in the prevention of mycosic ailments in people with congenital or acquired immune compromise.

The compounds of the invention are not limited to a pharmaceutical usage, they can be equally used as fungicides in domains other than pharmaceutical.

The invention thus has as its object as anti-fungal compounds, the compounds of formula (I) as well as their addition salts with the acids.

The invention equally has as its object the compounds of formula (I), as medicines.

The invention has very particularly as its object pharmaceutical compositions containing at least one compound of formula (I) or one of its addition salts with pharmaceutically acceptable acids as active ingredient.

These compounds can be administered by oral, rectal, parenteral route or by local route by topical application on the skin and the mucous membranes, but the preferred route is the oral route.

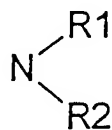
They can be solid or liquid and be presented in pharmaceutical forms currently used in human medicine, like for example, simple or sugar

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2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034 2035 2036 2037 2038 2039 2040 2041 2042 2043 2044 2045 2046 2047 2048 2049 2050 2051 2052 2053 2054 2055 2056 2057 2058 2059 2060 2061 2062 2063 2064 2065 2066 2067 2068 2069 2070 2071 2072 2073 2074 2075 2076 2077 2078 2079 2080 2081 2082 2083 2084 2085 2086 2087 2088 2089 2090 2091 2092 2093 2094 2095 2096 2097 2098 2099 2100 2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2113 2114 2115 2116 2117 2118 2119 2120 2121 2122 2123 2124 2125 2126 2127 2128 2129 2130 2131 2132 2133 2134 2135 2136 2137 2138 2139 2140 2141 2142 2143 2144 2145 2146 2147 2148 2149 2150 2151 2152 2153 2154 2155 2156 2157 2158 2159 2160 2161 2162 2163 2164 2165 2166 2167 2168 2169 2170 2171 2172 2173 2174 2175 2176 2177 2178 2179 2180 2181 2182 2183 2184 2185 2186 2187 2188 2189 2190 2191 2192 2193 2194 2195 2196 2197 2198 2199 2200 2201 2202 2203 2204 2205 2206 2207 2208 2209 2210 2211 2212 2213 2214 2215 2216 2217 2218 2219 2220 2221 2222 2223 2224 2225 2226 2227 2228 2229 2230 2231 2232 2233 2234 2235 2236 2237 2238 2239 2240 2241 2242 2243 2244 2245 2246 2247 2248 2249 2250 2251 2252 2253 2254 2255 2256 2257 2258 2259 2260 2261 2262 2263 2264 2265 2266 2267 2268 2269 2270 2271 2272 2273 2274 2275 2276 2277 2278 2279 2280 2281 2282 2283 2284 2285 2286 2287 2288 2289 2290 2291 2292 2293 2294 2295 2296 2297 2298 2299 2300 2301 2302 2303 2304 2305 2306 2307 2308 2309 2310 2311 2312 2313 2314 2315 2316 2317 2318 2319 2320 2321 2322 2323 2324 2325 2326 2327 2328 2329 2330 2331 2332 2333 2334 2335 2336 2337 2338 2339 2340 2341 2342 2343 2344 2345 2346 2347 2348 2349 2350 2351 2352 2353 2354 2355 2356 2357 2358 2359 2360 2361 2362 2363 2364 2365 2366 2367 2368 2369 2370 2371 2372 2373 2374 2375 2376 2377 2378 2379 2380 2381 2382 2383 2384 2385 2386 2387 2388 2389 2390 2391 2392 2393 2394 2395 2396 2397 2398 2399 2400 2401 2402 2403 2404 2405 2406 2407 2408 2409 2410 2411 2412 2413 2414 2415 2416 2417 2418 2419 2420 2421 2422 2423 2424 2425 2426 2427 2428 2429 2430 2431 2432 2433 2434 2435 2436 2437 2438 2439 2440 2441 2442 2443 2444 2445 2446 2447 2448 2449 2450 2451 2452 2453 2454 2455 2456 2457 2458 2459 2460 2461 2462 2463 2464 2465 2466 2467 2468 2469 2470 2471 2472 2473 2474 2475 2476 2477 2478 2479 2480 2481 2482 2483 2484 2485 2486 2487 2488 2489 2490 2491 2492 2493 2494 2495 2496 2497 2498 2499 2500 2501 2502 2503 2504 2505 2506 2507 2508 2509 2510 2511 2512 2513 2514 2515 2516 2517 2518 2519 2520 2521 2522 2523 2524 2525 2526 2527 2528 2529 2530 2531 2532 2533 2534 2535 2536 2537 2538 2539 2540 2541 2542 2543 2544 2545 2546 2547 2548 2549 2550 2551 2552 2553 2554 2555 2556 2557 2558 2559 2560 2561 2562 2563 2564 2565 2566 2567 2568 2569 2570 2571 2572 2573 2574 2575 2576 2577 2578 2579 2580 2581 2582 2583 2584 2585 2586 2587 2588 2589 2590 2591 2592 2593 2594 2595 2596 2597 2598 2599 2600 2601 2602 2603 2604 2605 2606 2607 2608 2609 2610 2611 2612 2613 2614 2615 2616 2617 2618 2619 2620 2621 2622 2623 2624 2625 2626 2627 2628 2629 2630 2631 2632 2633 2634 2635 2636 2637 2638 2639 2640 2641 2642 2643 2644 2645 2646 2647 2648 2649 2650 2651 2652 2653 2654 2655 2656 2657 2658 2659 2660 2661 2662 2663 2664 2665 2666 2667 2668 2669 2670 2671 2672 2673 2674 2675 2676 2677 2678 2679 2680 2681 2682 2683 2684 2685 2686 2687 2688 2689 2690 2691 2692 2693 2694 2695 2696 2697 2698 2699 2700 2701 2702 2703 2704 2705 2706 2707 2708 2709 2710 2711 2712 2713 2714 2715 2716 2717 2718 2719 2720 2721 2722 2723 2724 2725 2726 2727 2728 2729 2730 2731 2732 2733 2734 2735 2736 2737 2738 2739 2740 2741 2742 2743 2744 2745 2746 2747 2748 2749 2750 2751 2752 2753 2754 2755 2756 2757 2758 2759 2760 2761 2762 2763 2764 2765 2766 2767 2768 2769 2770 2771 2772 2773 2774 2775 2776 2777 2778 2779 2780 2781 2782 2783 2784 2785 2786 2787 2788 2789 2790 2791 2792 2793 2794 2795 2796 2797 2798 2799 2800 2801 2802 2803 2804 2805 2806 2807 2808 2809 2810 2811 2812 2813 2814 2815 2816 2817 2818 2819 2820 2821 2822 2823 2824 2825 2826 2827 2828 2829 2830 2831 2832 2



in which R, R3, R4, T, W, Y and Z retain their prior meaning, with the action of an amine or an amine derivative likely to introduce



the radical

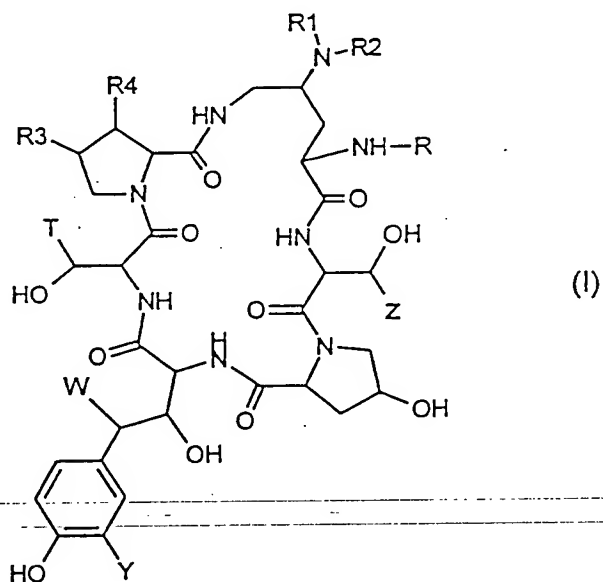
in which R1 and R2 retain their prior meaning and if desired the action of a reduction agent

and/or a functionalisation agent of the amine,

and/or an acid to form the salt of the obtained product,

and/or a separation agent of the different isomers obtained,

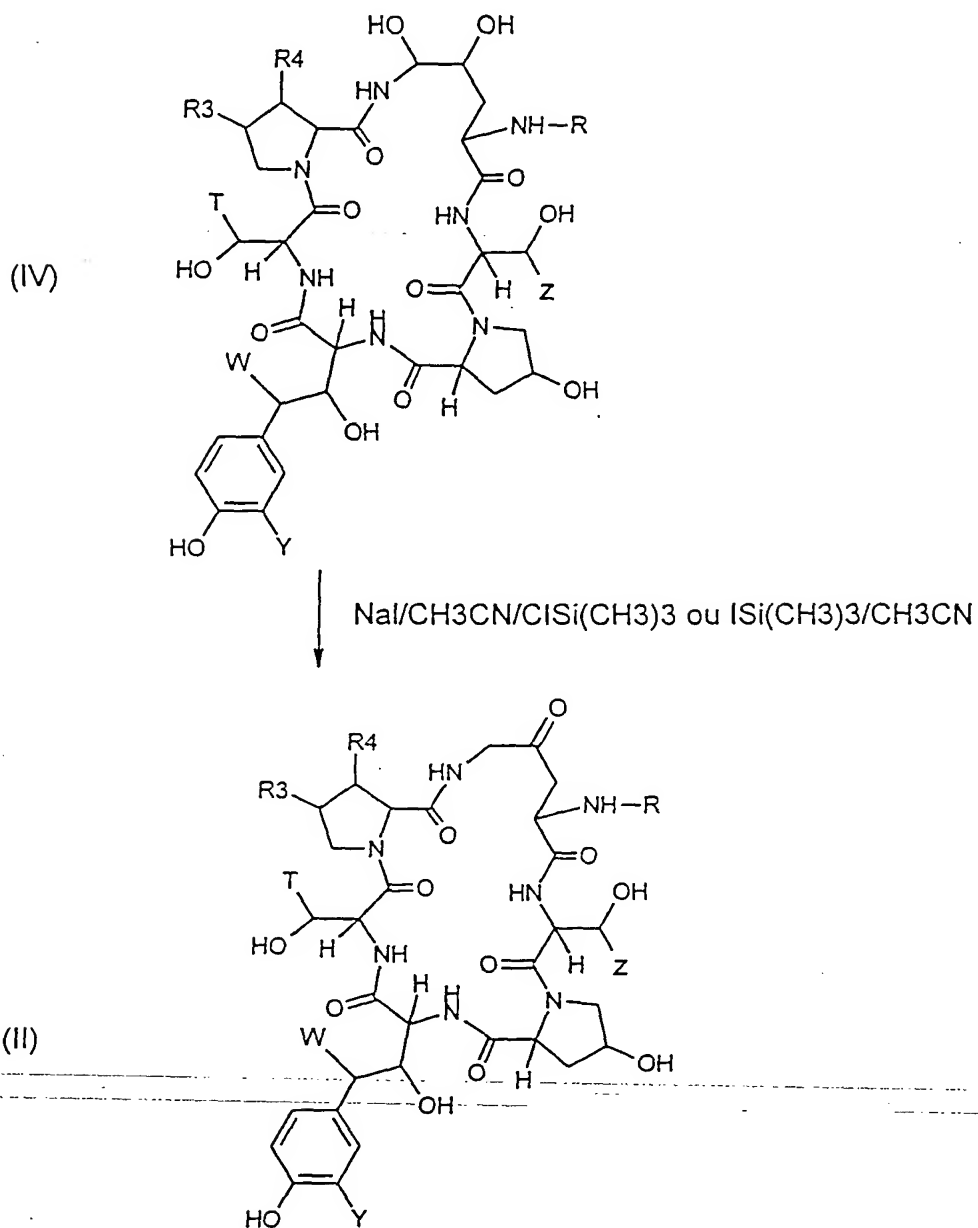
and thus obtains the sought formula (I) compound



in which R1, R2, T, W, Y, R and Z retain their prior meaning in all of its possible isomer forms as well as their compounds and/or in the form of salts with the acids.

The formula (II) compounds used as initial compounds of the process of the invention are novel products and are themselves an object of the

present invention, their preparation given in the experiment section can be schematised as follows:



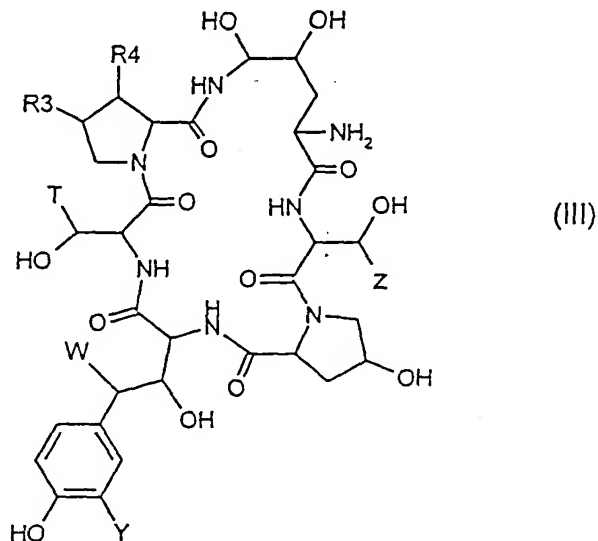
Isi-(CH₃)₃ or any other Lewis acid can be used.

A detailed example of the preparation of the compound of formula (II) is given in the experiment section, and the invention has more particularly as its object as novel chemical product 1-[4-oxo-N²-(12-methyl-1-oxotetradecyl) L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B.

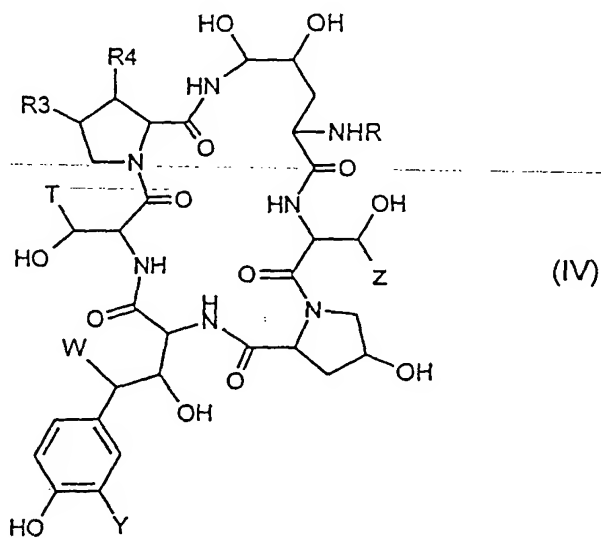
The product (IV) corresponding to the initial product of preparation 1 is a known product described and claimed in the European patent 438813.

The following examples illustrate the invention without at the same time limiting it.

The invention equally has as its object a preparation process characterised in that a formula (III) compound is submitted



in which the different substituents retain their prior meaning with the action of an agent capable of replacing NH_2 with NHR , R retaining its prior meaning to obtain the formula (IV) compound



in which the different substituents retain their prior meaning and are submitted to the action of silyl trimethyl iodide to obtain the compound of formula (II).

The compounds of formula (III) used as initial products are novel products and are themselves an object of the present invention. An example of preparation of the formula (III) compound is given hereafter in the experiment section.

The invention has more particularly as its object the deoxymulundocandin nucleus, compound of formula (III) the preparation of which is given hereafter in the experiment section.

The formula (IV) compounds as described above, with the exception of mulundocandin and deoxymulundocandin are novel products and are in themselves an object of the present invention.

The invention has more particularly as its object the compounds of formula (IV) whose preparation is given in the experiment section.

These following examples illustrate the invention without at the same time limiting it.

PREPARATION 1 : 1-[N2-(12-methyl-1-oxotetradecyl)-4-oxo-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B.

1g of 1-[(4R,5R)-4,5-dihydroxy-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B is introduced under magnetic stirring and under nitrogen atmosphere into 25ml of acetonitrile. 455µl of trimethylsilyl iodide is added. It is heated at 55°C for 40 minutes. It is hydrolysed with a solution of sodium thiosulphate at 3%. After 10 minutes of stirring, it is dried under reduced pressure and purified by chromatography on silica. 62% of sought product is obtained.
CCM: $r_f = 0.25$ (eluent: CH₂Cl₂-MeOH-H₂O 86-13-1).

EXAMPLE 1 : Trifluoroacetate of 1-[4-amino-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B (isomer B).

50mg of the product of preparation 1 is introduced into 2.5ml of methanol in the presence of 4A activated siliporite. 158mg of ammonium acetate at 20°C is added. The obtained solution is heated at 50°C and 5.5mg of NaBH₃CN is added. It is stirred for 3 hours 15 minutes. 1ml of distilled water is added and the solution is concentrated dry. 166mg of product is obtained that is purified by HPLC (C₁₈) by eluting with the compound CH₃CN-H₂O-TFA (50-50-0.02). 17mg of sought product is obtained.

MH⁺ = 975.

EXAMPLE 2 : Trifluoroacetate of 1-[4-[[2-dimethylaminoethyl]-amino-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B (isomers A and B).

80mg of the product of preparation 1, is introduced at 20°C into a solution containing 1ml of methanol, 160µl of 2-dimethyl-aminoethylamine, 8ml of a solution 1M of hydrochloric acid in methanol in the presence of 4A siliporite. 35mg of sodium cyanoborohydride is introduced and stirred for 20 hours at 20°C. It is filtered, washed in methanol and concentrated dry. 325mg of product are obtained that is purified by HPLC (C₁₈) (eluent : CH₃CN-H₂O-TFA 45-55-0.02 then CH₃CN-H₂O- TFA 42-58-0.02). 8.1mg of sought isomer A product and 9.4mg of isomer B sought product are obtained.

Mass Spectrometry:

MH⁺ = 1046

MNa⁺ = 1068

EXAMPLE 3 : Trifluoroacetate of 1-[4-[(3-aminopropyl)amino]-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxy-phenyl)-L-threonine]-5-L-serine echinocandin B (A and B isomers).

30cm³ of a 1M solution of hydrochloric acid is added at 0°C in methanol into a solution containing 200mg of the product of preparation 1, 2 ml of methanol and 300µl of diaminopropane. It is stirred for 15 minutes at 0°C and 84mg of sodium cyanoborohydride at 95% is added. It is stirred for 6

hours at ambient temperature and dried under reduced pressure. The obtained residue is made into a paste in acetonitrile, spun and dried under reduced pressure. 312mg of product that is purified by HPLC (C₁₈) (eluent : CH₃CN-H₂O-TFA 45-55-0.02) and 15mg of isomer A and 10mg of isomer B is obtained.

Mass Spectrometry:

MH⁺ = 1032.

EXAMPLE 4 : (Z+E) Trifluoroacetate of 1-[4-[(4.5-dihydro-1H-imidazol-2-yl)hydrazono]-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B.

350mg of the product of preparation 1, 12ml of methanol and 130mg of 2-hydazino 2-imidazoline hydrobromide is kept at reflux for 2 hours whilst stirring. After evaporating dry, 510mg of product is obtained that is purified by chromatography on silica by eluting with the compound CH₂-Cl₂-MeOH-H₂O (86-13-1) then by semi-preparative (C₁₈) HPLC by eluting with the compound CH₃CN-H₂O-TFA (55-45-0.02). 133mg of sought product is thus obtained.

Mass spectrometry:

MH⁺ = 1056

MNa⁺ = 1078

EXAMPLE 5: (Z) 1-[4-[(2-Hydroxyethoxy) imino]-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B and corresponding E isomer.

a mixture of 36mg of O-(2-hydroxyethyl) hydroxylamine, 5ml of ethanol, 12μl of pyridine, 4μl of pure acetic acid and 150mg of the product of preparation 1 is kept at reflux for 4 hours. 205mg of product that is purified by chromatography on silica by eluting with the methylene chloride-methanol-water (86-13-1) mixture. 2 products of rf=0.2 and 0.25 (isomer Z and isomer E) are isolated.

Mass spectrometry:

MH⁺ = 1033

MNa⁺ = 1055

EXAMPLE 6: (E) 1-[4-(hydroxyimino)-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B and corresponding Z isomer.

A mixture containing 200mg of the product of preparation 1, 8ml of ethanol, 36mg of hydroxylamine hydrochloride is left for 1 hour at reflux whilst stirring. It is dried and purified by chromatography HPLC (C₁₈) (eluent CH₃CN-H₂O 60-40). 72mg of Z isomer and 60mg of E isomer is obtained.

Mass spectrometry:

MH⁺ = 989

MNa⁺ = 1011

EXAMPLE 7 : Trifluoroacetate of 1-[4-(hydroxyamino)-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B (isomer A and isomer B).

70mg of E+Z oxime mixture obtained in the previous example, 1cm³ of trifluoroacetic acid, 12mg of sodium cyanoborohydride at 95% mixture is stirred for 3 hours. It is dried under reduced pressure. It is purified by HPLC (C₁₈). The products sought are obtained.

Mass spectrometry:

MH⁺ = 991

MNa⁺ = 1013

EXAMPLE 8 : (Z) Chlorohydrate of 1-[(S)-N2-(12-methyl-1-oxotetradecyl)-4-[[[(3-piperidinyl)oxy] imino]-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L serine echinocandin B.

Stage A:

146mg of the product of preparation 1 and 60μl of acetic acid is added to a solution containing 45mg of R-3-(aminooxy)-1-piperidine phenylmethyl carboxylate and 2 ml of methanol. It is stirred for 2 hours at ambient temperature. It is concentrated, purified by chromatography on silica by eluting with the 98-2 methylene chloride-methanol compound. The sought product is thus obtained.

Mass spectrometry:

$MH^+ = 1206$

$MNa^+ = 1228$

Stage B:

A compound containing 61mg of the product prepared in stage A, 20mg of palladium on carbon and 1 ml of acetic acid is placed under hydrogen atmosphere and stirred vigorously for 5 hours. It is filtered and concentrated. 65% of sought product is obtained.

Mass spectrometry:

$MH^+ = 1072$

EXAMPLE 9 : Trifluoroacetate of 1-[4-[(2-aminoethyl) amino]-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L serine echinocandin B (isomer A and isomer B).

To the solution of 300mg of preparation 1 in 6ml of methanol in the presence of 375 μ l of ethylenediamine is added 63ml of a solution of 1M of hydrochloric acid in methanol. After 15 minutes of agitation, 126mg of sodium cyanoborohydride ($NaBH_3CN$) is added. The reaction medium is stirred for 5 hours. It is filtered and dried, the products purified by HPLC (C_{18}) by eluting with the $CH_3CN - H_2O - TFA$ (40-60-0.02) mixture. The sought products are thus obtained.

Mass spectrometry:

$MH^+ = 1018$

$MNa^+ = 1040$

EXAMPLE 10: (E) 1-[4-[(2-bromoethoxy) imino)-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B and corresponding Z isomer.

402mg of bromo-2-ethoxyamine bromhydrate is added to a solution containing 710mg of the product of preparation 1 and 28ml of absolute methanol. The mixture is brought to reflux for 55 minutes. It is concentrated under reduced pressure. The obtained product is purified by flash chromatography on silica by eluting with the (9-1) methylene chloride-methanol compound. The sought products isomer A: $R_f=0.54$, isomer B: $R_f = 0.47$ are obtained.

Mass spectrometry:

$MH^+ = 1095$

$MNa^+ = 1117$

EXAMPLE 11 : (+) Trifluoroacetate of 1-[4-[(aminoiminomethyl)hydrazono]-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L serine echinocandin B.

162mg of aminoguanidine hydrochloride is added to a solution containing 260mg of the product of preparation 1 and 10ml of n-butanol. The reaction medium is brought to reflux for 2 hours 30 minutes. It is concentrated under reduced pressure. The obtained product is purified by semi-preparative HPLC. 225mg of product in a 50/50 mixture of isomers is obtained.

Mass spectrometry:

$MH^+ = 1030$

$MNa^+ = 1052$

EXAMPLE 12 : (Z) Trifluoroacetate of 1-[4-[[2-(dimethylamino)ethoxyimino]-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B and corresponding E isomer.

80.5mg of the product of example 10 are introduced into 32ml of an ethanolic solution of dimethylamine. The reaction medium is brought to reflux for 45 minutes. It is concentrated. The obtained product is purified by HPLC (C₁₈) (CH₃CN-H₂O - TFA 60-40-0.02). The sought products are thus obtained.

Mass spectrometry:

$MH^+ = 1060$

EXAMPLE 13 : (E) Trifluoroacetate of 1-[4-[[2-aminoethoxy]-imino]-N2-(12-methyl-1-oxotetradecyl)-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B and corresponding Z isomer.

50mg of the product of example 10 is introduced into ammonia. It is stirred under pressure for 16 hours whilst allowing it to come to ambient temperature. The reaction medium is again placed in the (45-55) CH₃CN-H₂O compound to be purified by HPLC (C₁₈). The sought products are obtained.

Mass spectrometry:

$MH^+ = 1032$.

Preparation 2: deoxymulundocandin "nucleus"

2g of deoxymulundocandin are dissolved in 20ml of DMSO. This solution is poured into a suspension containing 120g of FH2264 *Utahensis* actinoplanes in 870ml of a KH_2PO_4 , K_2HPO_4 (pH: 6.8) buffer. The reaction medium is stirred for 70 hours at 30°C. It is filtered. The mycelium is washed with the phosphate buffer (pH: 6.8). The washing liquids and the filtrate are joined. The obtained product is chromatographed on a DIAION HP 20, resin and a product is obtained that is used as hereafter.

EXAMPLE 14 : Trifluoroacetate of 1-[4-[(2-aminoethyl) amino] N2-[[4'-(octyloxy)][1.1'-biphenyl]-4-yl]carbonyl]-L-ornithine] 4-[4-(4-hydroxyphenyl)-L-threonine]-5-L serine echinocandin B (isomer A)
Stage A: 1-[(4R,5R)-4,5-dihydroxy-N2-[[4'-(octyloxy)][1.1'-biphenyl]-4-yl]carbonyl]-L-ornithine]-4-[4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B

1-Preparation of the ester

632g of 2,3,4,5,6 pentafluorophenol is added in 695mg of N, N'-dicyclohexylcarbodiimide to 1g of 4'-(octyloxy)-[1.1'-biphenyl]-4-carboxylic acid in 22ml of tetrahydrofuran, stirred for 22 hours at ambient temperature, filtered, the solvents are eliminated under reduced pressure, the residue is placed into ether, stirred at about 35°C, filtered, the solvent is evaporated, it is dried and 1.46g of expected product is obtained, used as it is.

2-Coupling

677mg of deoxymulundocandin <<nucleus>> obtained in preparation-2 is introduced, into 16ml of DMF. The obtained solution is stirred for 5 minutes and 793g of 4'-(octyloxy)-[1.1'-biphenyl]-4-pentafluorophenyl carboxylate obtained above is added.

The reaction compound is stirred and kept under nitrogen atmosphere for 24 hours. It is filtered and concentrated. The residue is placed into ether, triturated, stirred for 25 minutes, spun, washed with ethylic ether, chromatographed on silica by eluting with the (86/13/1) then (80/20/1)

methylene chloride, methanol, water mixture. The sought product is thus obtained. Yield 73%.

Stage B: 1-[N2-[[4'-(octyloxy)-[1.1'-biphenyl]-4-yl]carbonyl]-4-oxo-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B

311µl of trimethylsilyl iodide is added to a suspension containing 809mg of the product of stage A and 19ml of acetonitrile. The reaction medium is stirred for 15 minutes at 60°C under nitrogen atmosphere. The compound is poured into a sodium thiosulphate saturated solution. The residue obtained is evaporated and chromatographed on silica, by eluting with the 86/13/1 methylene-chloride methanol water compound. The sought product is obtained. Yield 55%.

Stage C: 1-[4-[(2-aminoethyl) amino]-N2-[[4'-(octyloxy)[1.1'-biphenyl]-4-yl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L serine echinocandin B (isomer A) trifluoroacetate

560µl of acetic acid are added to a solution containing 900mg of the product of the preceding stage, 16ml of methanol and 250µl of diamine ethylene. It is stirred for 15 minutes and 64mg of sodium cyanoborohydruce is added. It is stirred for 18 hours. It is filtered and concentrated. The residue is placed in a minimum of water, triturated, spun and purified by preparative HPLC by eluting with the compound CH₃CN/H₂O/TFA/ (55-45-0.2). The sought product is obtained. Yield 26%.

Spectrum RMN CDCl₃

9.07 (m wide) 1H; 8.48 (dl, J=8) 1H; 8.00 (dl, J=8) 2H; 7.96 (dl, J=8.5) 2H; 7.71 (dl, J=8.5) 2H; 7.64 (dl, J=8.5) 2H; 7.60 (dl, J=9) 1H; 7.37 (dl, J=9.5) 1H; 7.02 (dl, J=8.5) 2H; 6.97 (dl, J=8.5) 2H; 6.65 (dl, J=8.5) 2H; 4.90 (m) 1H; 4.77 (m) 1H; 4.66 (m) 1H; 4.45 (m) 1H; 4.42 (m) 1H; 4.39 (m) 1H; 4.34 (sl) 1H; 4.26 (m) 1H; 4.22 (m) 1H; 4.08 (m) 1H; 4.01 (t, J=6.5) 2H; 3.88 (m) 3H; 3.70 (m) 2H; 3.51 (m) 2H; 3.48 (m) 1H; 3.31 (m) 2H; 3.28 (m) 1H; 3.16 (m) 2H; 2.53 (dd, J=6 et 13.5) 1H; 2.44 (dd, J=7.5 et 13.5) 1H; 2.27 (m) 1H; 2.25 (m) 1H; 2.15 (m) 2H; 1.94 (m) 1H; 1.74 (m) 2H; 1.44 (m) 2H; 1.22 to 1.40 (m) 8H; 1.13 (d, J=6) 3H; 0.99 (d, J=6.5) 3H; 0.88 (t, J=7) 3H.

EXAMPLE 15: 1-[4-[(aminoiminomethyl)hydranol]-n2-[[4-[4-(4-pentyloxy)-phenyl]-1-piperazinyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B

Stage A: 1-[(4R, 5R)-4.5-dihydroxy-N2-[[4-[4-[4-(pentyloxy)phenyl]-1-piperazinyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxy-phenyl)-L-threonine]-5-L-serine echinocandin B

1-Preparation of the ester

55mg of pentafluorophenol and 61mg of N, N' dicyclohexyl carbodiimide is added to a mixture of 100mg of [4-[4-[4-(pentyloxy)phenyl]-1-piperazinyl]phenyl]carboxylic acid and 3ml of tetrahydrofurane. The reaction compound is stirred at 20°C for 16 hours, filtered, washed with THF and concentrated dry. It is placed in diethyl ether, filtered, washed and concentrated. 71mg of product is obtained.

2-Coupling

A suspension containing 71mg of the ester above, 70mg of deoxymulundocandin <<nucleus>> obtained as in preparation 2, 2.5ml of DMF in the presence of 4A activated siliporite is stirred at 20°C for one night. It is concentrated, the product obtained is placed in ether and filtered. A product is obtained that is chromatographed on silica by eluting with the mixture acetonitrile/water/trifluoroacetic acid (60-40-0.02). 30mg of sought product is thus obtained.

Stage B: 1-[N2-[4-[4-[4-(pentyloxy)phenyl]-1-piperazinyl]-phenyl]-carbonyl]4-oxo-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandin B

1-Preparation of the ester

a mixture of 1g of the product of stage A; 25 ml of acetonitrile, in the presence of 4A activated siliporite is heated to 55°C. 430ml of trimethylsilane iodide is added. It is stirred for 45 minutes then 150µl of an aqueous solution of sodium thiosulphate at 30% is added. It is stirred for 40 minutes at 20°C and concentrated. The dry extract is placed in water, stirred for 1 hour at 20°C spun and washed. A product is obtained that is chromatographed on silica by eluting with the compound methylene chloride-methanol-water (86/13/1). 497mg of sought product are obtained. Yield 42%.

Stage C: 1-[4-[(aminoiminomethyl)hydrazono]-N2-[4-[4-[4-(pentyloxy)-phenyl]-1-piperazinyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B

A suspension containing 400mg of the product of stage B, 4.8ml of n-butanol and 221 mg of aminoguanidine hydrochloride is heated at 130°C for 3 hours. It is concentrated and 705mg of a product is obtained that is chromatographed on silica by eluting with the methylene chloride methanol

compound 85/15, then by semi-preparative HPLC (kromasil C18) with a 40.60.0.02) acetonitrile/water/trifluoroacetic acid compound. 64mg of sought product is thus obtained.

Spectrum RMN CDCl_3

10.75 (s) 0.66H ; 10.45 (s) 0.33H ; 8.39 (d, J=8) 0.33H ; 8.34 (m) 1H ; 8.10 (d, J=7.5) 0.66H ; 8.08 (d, J=8) 0.33H ; 7.99 (d, J=8.5) 0.66H ; 7.74 (d, J=8.5) 1.33H ; 7.71 (d, J=8.5) 0.66H ; 7.60 (d, J=8.5) 0.66H ; 7.50 (m) 1.33H ; 7.00 (m) 6H ; 6.86 (d, J=8.5) 2H ; 6.65 (d, J=8) 2H ; 5.08 (dt, J=2 et 11.5) 0.66H ; 4.94 (m) 1H ; 4.88 (m) 0.33H ; 4.75 (dm, J=8) 0.33H ; 4.67 (dd, J=3 et 7.5) 0.66H ; 4.43 (m) 1H ; 4.38 (m) 1.66H ; 4.33 (m) 0.66H ; 4.26 to 4.20 (heavy) 2.33H ; 4.12 (d, J=9) 0.66H ; 4.00 to 3.68 (heavy) 7.33H ; 3.90 (t, J=7) 2H ; 3.62 (d, J=12) 0.33H ; 3.43 (swide) 2H ; 3.30 to 3.20 (m) 1H ; 3.20 (swide) 2H ; 2.91 (d, J=14) 0.66H ; 2.86 (m) 0.33H ; 2.76 (m) 0.33H ; 2.63 (dd, J=14 et 12.5) 0.66H ; 2.52 (dt, J=6 et 13) 1H ; 2.44 (dd, J=8 and 13) 1H ; 2.35 (m) 0.33H ; 2.25 (m) 1.66H ; 1.93 (twide, J=13) 1H ; 1.69 (m) 2H ; 1.42 to 1.30 (heavy) 4H ; 1.15 (d, J=6) 1.98H ; 1.10 (, J=6) 0.99H ; 0.98 (d, J=6.5) 3H ; 0.90 (t, J=7) 3H.

EXAMPLE 16: 1-[4-[(2-aminoethyl)amino]-N2-[4-[4''-(pentyloxy)][1.1':4'1''-terphenyl]-4-yl]carbonyl]-L-ornithine]-4-[4-(hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B (isomer A and isomer B).

Operating as previously, from deoxy-mulundocandin <<nucleus>> prepared as indicated in preparation 2 by obtaining 1-[(4R, 5R)-4.5-dihydroxy-N2-[[4''-(pentyloxy)][1.1': 4'.1''-terphenyl]-4-yl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B and the corresponding 4-oxo derivative as intermediate product, the sought product is obtained.

Spectrum RMN CDCl_3

9.00 (wide) 1H ; 8.37 (dl, J=8.5) 1H ; 8.28 (m) 1H ; 8.10 (dl, J=6) 1H ; 8.02 (dl, J=8) 2H ; 7.82 (m) 4H ; 7.73 (dl, J=8) 2H ; 7.66 (dl, J=8) 2H ; 7.38 (dl, J=9) 1H ; 7.32 (dl, J=9) 1H ; 7.03 (dl, J=8.5) 2H ; 6.96 (dl, J=8) 2H ; 6.66 (dl, J=8) 2H ; 5.03 (m) 1H ; 4.84 (m) 1H ; 4.67 (m) 1H ; 4.45 (m) 2H ; 4.36 (dd, J=7.5 and 10.5) 1H ; 4.23 (m) 2H ; 4.18 (sl) 1H ; 4.04 (m) 1H ; 4.02 (t, J=6.5) 2H ; 4.00 (m) 1H ; 3.87 (dl, J=9.5) 1H ; 3.76 (m) 1H ; 3.72 (m) 2H ; 3.55 (m) 1H ; 3.44 (m) 1H ; 3.35 (m) 2H ; 3.30 (m) 1H ; 3.19 (m) 2H ; 3.12 (m) 1H ; 2.53 (m) 1H ; 2.45 (m) 1H ; 2.12 to 2.30 (m) 3H ; 1.90 to 2.05 (m) 2H ; 1.74 (m) 2H ; 1.30 to 1.55 (m) 4H ; 1.20 (d, J=5.5) 3H ; 0.96 (d, J=6.5) 3H ; 0.91 (t, J=7) 3H.

EXAMPLE: Pharmaceutical composition:

Tablets have been prepared containing:

-The product of example 14.....150mg

-Excipient q.s.p.....1g

(Detail of the excipient: starch, talc, magnesium stearate).

PHARMACOLOGICAL STUDY

A – Inhibition of the glucane synthesis of *Candida albicans*.

The membranes of *Candida albicans* are purified according to the process described by Tang and al Antimicrob. Agents Chemother 35, 99-103, 1991. 22.5µg of membrane proteins are incubated in a mixture of 2Mm of ¹⁴C-UDP glucose (specific activity = 0.34mCi./mmol, 50µg of α-amylase, 1Mm of dithiotreitol (DTT), 1Mm EDTA, 100Mm NaF, 7µM of GTP-γ-S, 1M of sucrose and 50Mm OF Tris-HCL (pH 7.8) in a volume of 100µl. The medium is incubated at 25°C for 1 hour and the reaction terminated by addition of TCA to a final concentration of 5%. The reaction medium is transferred onto a pre-humidified glass fibre filter. The filter is washed, dried and its radioactivity is counted.

Mulundocandin is used as positive control.

The control of the medium is carried out with the same quantity of DMSO 1%. The obtained results show that the products of the invention present a good activity in this test, particularly the products of examples 9, 11, and 14.

B – activity on the enzyme *Aspergillus fumigatus*.

The enzyme is prepared according to the Beaulieu et al. (Antimicrob. Agents Chenother 38, 937-944, 1994) process.

The protocol used is identical to the protocol described above for the enzyme *Candida albicans* except that dithiotreitol is not used in the reaction medium.

The products present a good activity in this test.
